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EXAMINER	
JOHNSON, N	
ART UNIT	**PAPER NUMBER**
1806	12

DATE MAILED: 01/07/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/29/97 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~days from the~~ date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948. slash
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims ~~1-5~~ 6, 8-5 are pending in the application.
   Of the above, claims 16-28, 38-50 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 6, 8-15, 29-37 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. With the authority of the Director's Office, the petition filed on 9/29/97 has been treated as a request for reconsideration which is hereby granted. Consequently, the restriction requirement into Groups I-IV is hereby withdrawn. The requirement for the election of species is maintained. The applicant, in Paper 7, filed 12/17/96 elected the examination of Species A: wherein the tumor factor antagonist is an antibody.

2. Claims 1-5 and 7 have been canceled.
Claims 6, 8-11, 13-16, 23, 28-33 and 35-37 have been amended.
Claims 6 and 8-50 are pending.
Claims 16-28 and 38-50, drawn to non-elected inventions, are withdrawn from examination
Claims 6, 8-15 and 29-37 are examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 11, 14-15, 33 and 36-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Support for the recitation "competitively inhibits binding of TNFα to monoclonal antibody cA2" is not found in the specification. This recitation is considered new matter.

5. The rejection of claims 9-10, 12-15, 31-32 and 34-37 under 35 U.S.C. 112, second paragraph, is made and maintained.

The rejection of claims 8 and 9 for the recitation "fragments thereof" is withdrawn in view of the amendments to the claims.

Claims 9, 12-15, 31 and 34-37 are vague and indefinite in the recitation "chimeric." The applicant argues that the specification provides a definition of "chimeric." This is not found persuasive, as all of the definitions provided in the specification are open ended, thus not setting the metes and bounds of a "chimeric antibody." See, for example p. 10 "As used herein the term 'chimeric antibody' ***includes*** monovalent, divalent or polyvalent antibodies," or, p. 11 "The anti-TNF chimeric antibodies ***can comprise*** .." (emphasis added). The applicant is advised to amend the claims to recite "a chimeric antibody comprised of antigen binding region derived from a non-human antibody specific for TNF and human constant region."

The rejection of claims 11 and 14 for the recitation "binds to the epitope of" is withdrawn in view of the amendments to the claims.

Claims 10, 13, 32 and 35 are vague and indefinite in the recitation "binds to one or more epitopes." By art accepted definition, a single antibody binds to one epitope. Thus, it is unclear how the claimed antibody can bind to one or more epitopes.

The rejection of claim 11 for the recitation "A2" is withdrawn.

Claims 14-15 and 36-37 are rejected for the recitation "cA2." "CA2" is vague and indefinite as it is unclear whether cA2 designates a monoclonal chimeric antibody secreted by a unique cell line or whether it designates any chimerization of the A2 monoclonal antibody.

The rejection of claims 10 and 13 for the recitation "binds to one or more amino acid residues of TNFα selected from the group consisting of about 87-108 and about 59-80" is withdrawn in view of the amendments to the claims.

The rejection of claims 6 and 7 for the recitation "thrombotic disorder" is withdrawn in view of the amendments to the claims.

6. The rejection of claims 11, 14-15, 33 and 36-37 under 35 U.S.C. § 112, first paragraph, as

failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials is maintained. The applicant argues that the subject application incorporates by reference information on the A2 and cA2 monoclonal antibodies described in several pending and issued patent applications from which priority of the instant application does not depend. The applicant argues further that the cited applications provide a significant description of the properties of the cA2 and A2 antibodies and that with this information, screening for antibodies having the same or similar properties would be straightforward to one of skill in the art. This has been carefully considered and is not found persuasive. The applicant has not identified the specific facts in the four different patent applications, incorporated by references, that are relied on to provide enablement for claims drawn to the monoclonal antibodies A2 or cA2. The argument that the various specification provides an adequate description to enable one of skill in the art to obtain similar antibodies is not persuasive. The claims are drawn to monoclonal antibodies secreted by unique cell lines. Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally identical to those claimed. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas. Please note that the sequence of the entire immunoglobulin would also satisfy this enablement requirement. However, partial sequences do not provide adequate enablement, as the claims are drawn to an intact antibody molecule.

7. The rejection of claims 6, 8-15 and 29-37 under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure commensurate with the scope of the claims, is made and maintained.

The rejection of claims 6 and 29, broadly drawn to a method of treatment comprising the administration of a tumor necrosis factor "antagonist" is made and maintained. The applicant argues that it would not require undue experimentation to make and use "TNF antagonists" "since antibodies generally function by antagonizing or otherwise inhibiting the activity of its cognate antigen, it is expected, based on scientific reasoning, that the claimed invention works in the same manner using other antagonists." The application also argues that the specification discloses TNF antagonists to include anti-TNF antibodies, receptor molecules, agents which prevent or inhibit TNF synthesis or release, and agents which prevent or inhibit TNF receptor signaling. This has been carefully considered and is not found persuasive. By the applicant's own admission, they contemplate a "TNF antagonist" to encompass many classes of molecules (antibodies to receptors to agents that inhibit) that function to inhibit TNF activity via many different routes (antibody binding to cognate antigen; an agent inhibiting one of the multiple steps in receptor signaling; an agent inhibiting the synthesis of the TNF protein). Guidance for the making and using of this vary broad collection of molecules can not be drawn from the making and using of antibodies in the claimed method. Thus, one of skill in the art can not practice the claimed invention, without undue experimentation.

Claims 6, 8 and 29-30 are drawn to treatment methods comprising the administration of antagonists and/or antibodies to tumor necrosis factor and are broad enough to read on the administration of murine antibodies. U.S. Patent 5,698,195 (col. 3, line 37-40) notes the ineffectiveness of murine antibodies as in vivo therapeutic agents in humans. Thus, one of skill in the art could not practice the claimed invention commensurate with the scope of the claims with a reasonable expectation of success.

Claims 6, 8-15 and 29-37 are broadly drawn to a method of treating or preventing thrombosis. The specification demonstrates that the administration of anti-tumor necrosis α antibodies to rheumatoid arthritis patients results in a decrease in elevated fibrinogen levels to a range closer to "normal," "that the inhibition of the biological activity of tumor necrosis factor α reduces fibrinogen and platelets levels in individuals with active rheumatoid arthritis" (see p. 2, lines 14-18) . This showing is used to support claims broadly drawn to the treatment of "thrombosis." The applicant argues that "since platelet and fibrinogen play integral roles in thrombosis, this evidence would satisfy one of skill in the art that anti-TNF antibodies would likely be effective in the treatment of thrombosis. This is not found persuasive. Active rheumatoid arthritis is a distinct disease state, with unique pathological parameters that are known to be associated with the increased production of TNF (see U.S. Patent 5,698,195 col.9, line 55-65. Such results obtained with the administration of anti-TNF antibodies in rheumatoid arthritis can not be generalized to all types of thrombosis, were TNF production does not necessarily play a role in the pathology. Thus, it remains unpredictable that one of skill in the art could practice the claimed invention commensurate with the scope of the claims with a reasonable expectation of success and without undue experimentation

Claims 29-37 are broadly drawn to a "method of decreasing plasma fibrinogen in an individual suffering from or at risk of thrombosis." The specification discloses the inhibition of the biological activity of tumor necrosis factor α reduces fibrinogen and platelets levels in individuals with active rheumatoid arthritis" (see p. 2, lines 14-18). There is no evidence of record that individuals with active rheumatoid arthritis are suffering from or at risk of thrombosis. Thus, it is unpredictable that one of skill in the art could practice the claimed invention commensurate with the scope of the claims, reduce fibrinogen levels in individual suffering from or at risk of thrombosis

Claims 10, 13, 32 and 35 are drawn to antibodies that bind "one or more epitopes." It is art accepted that one antibody binds to one epitope. The specification provides no instruction for

the preparation of antibodies that bind to more than one epitope. Thus, one of skill in the art could not predictable make and use the claimed antibody.

The rejection of claim 6, drawn to a "method for treating or preventing thrombotic disorder," is withdrawn in view of the amendment to the claim.

The rejection of claims 8 and 9, drawn to "fragments thereof" of an anti-tumor necrosis antibody is withdrawn in view of the amendments to the claims.

The rejection of claims 10 and 13, drawn to antibodies that bind "to one or more amino acid residues of TNFα selected from the group consisting of about 87-108 and about 59-80," is withdrawn in view of the amendments to the claims.

8. The rejection of claim 6 rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,547,979 is withdrawn.

9. The rejection of claims 6 and 8-9 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Number 5,436,154 is withdrawn.

10. The rejection of claims 6 and 8 under 35 U.S.C. 102(b) as being anticipated by Squadrito et al. (Eur. J. Pharmacology 237:223-230, 1993) is withdrawn.

11. The rejection of claims 9-15 under 35 U.S.C. 103(a) as being unpatentable over either of U.S. Patent Number 5,436,154 or Squadrito et al. in view of WO 92/16553 is withdrawn.

12. Claims 29-30 are rejected under 35 U.S.C. 102(b) as being anticipated by van der Poll (Blood 83:446, 1994). Van der Poll discloses an *in vivo* method of decreasing plasma fibrinogen comprising the administration of an anti-TNF antibody that is the same as that claimed.

13. Claims 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over van der Poll (Blood 83:446, 1994) in view of WO 92/16553. The teachings of van der Poll, of a method for decreasing plasma fibrinogen comprising the administration of an anti-TNF antibody, have been previously discussed in the above paragraph. Van der Poll does not teach the use of the A2 antibody or the cA2 chimeric antibody in the method of treatment. However, WO 92/16553 teaches both the A2 and cA2 antibodies (see p. 9, line 29 and p. 61, line 21), antibodies which recognize an epitope containing TNF amino acid residues 87-108 or 59-80 (see p. 7, lines 29-32). It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the A2 and cA2 antibodies, as taught in WO 92/16553 in the treatment method taught in van der Poll, which utilize an anti-TNF monoclonal antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of WO 92/16553; on the high binding affinity of the A2 antibody (see p. 9, line 29) and the usefulness of chimeric antibodies, such as cA2, in overcoming the "problems of murine antibody immunogenicity" and to "provide reduced immunogenicity and increased neutralization activity" (see p. 7, lines 14-17).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Johnson whose telephone number is (703) 305-5860. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122.

This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Toni R. Scheiner

N. Johnson

TONI R. SCHEINER
PRIMARY EXAMINER
GROUP 1800

Nancy A. Johnson, Ph.D.
Patent Examiner, Group 1806
January 5, 1998